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# Accepted Manuscript



## Sensitive Troponin Assay and the Classification of Myocardial Infarction

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## Sensitive Troponin Assay and the Classification of Myocardial Infarction

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**Abstract**

**Background:** Lowering the diagnostic threshold for troponin is controversial because it may disproportionately increase the diagnosis of myocardial infarction in patients without acute coronary syndrome. We assessed the impact of lowering the diagnostic threshold of troponin on the incidence, management and outcome of patients with type 2 myocardial infarction or myocardial injury.

**Methods:** Consecutive patients with elevated plasma troponin I concentrations ( $\geq 50$  ng/L;  $n=2,929$ ) were classified as type 1 (50%) myocardial infarction, type 2 myocardial infarction or myocardial injury (48%) and type 3-5 myocardial infarction (2%) before and after lowering the diagnostic threshold from 200 to 50 ng/L with a sensitive assay. Event-free survival from death and recurrent myocardial infarction was recorded at one year.

**Results:** Lowering the threshold increased the diagnosis of type 2 myocardial infarction or myocardial injury more than type 1 myocardial infarction (672 *versus* 257 additional patients,  $P<0.001$ ). Patients with myocardial injury or type 2 myocardial infarction were at higher risk of death compared to type 1 myocardial infarction (37% *versus* 16%; RR 2.31, 95%CI 1.98-2.69), but had fewer recurrent myocardial infarctions (4% *versus* 12%; RR 0.35, 0.26-0.49). In patients with troponin concentrations 50-199 ng/L, lowering the diagnostic threshold was associated with increased healthcare resource utilization ( $P<0.05$ ) that reduced recurrent myocardial infarction and death for patients with type 1 myocardial infarction (31% *versus* 20%; RR 0.64, 0.41-0.99), but not type 2 myocardial infarction or myocardial injury (36% *versus* 33%; RR 0.93, 0.75-1.15).

**Conclusion:** Following implementation of a sensitive troponin assay, the incidence of type 2 myocardial infarction or myocardial injury disproportionately increased and is now as frequent as type 1 myocardial infarction. Outcomes of patients with type 2 myocardial infarction or myocardial injury are poor and do not appear to be modifiable following reclassification despite substantial increases in healthcare resource utilization.

## Introduction

The Universal Definition of Myocardial Infarction proposes a classification for patients with myocardial infarction based on etiology in order to accommodate more sensitive markers of myocardial necrosis.<sup>1</sup> The classification differentiates between type 1 myocardial infarction, due to thrombosis of an atherosclerotic plaque, and type 2 myocardial infarction due to an imbalance of myocardial blood supply and demand that may arise in many acute medical and surgical conditions. The expert consensus further defines evidence of myocardial necrosis in the absence of clinical evidence of myocardial ischemia as myocardial injury. Whilst this classification has been used in recent clinical trials to refine clinical outcomes<sup>2-4</sup>, type 2 myocardial infarction and myocardial injury are difficult to distinguish or diagnose definitively, and the frequency in clinical practice and implications of these diagnoses are uncertain.<sup>5,6</sup>

Following improvements in assay performance, a sensitive troponin assay was introduced into our institution.<sup>7,8</sup> The validation and subsequent implementation of this assay provided an opportunity to assess the impact of lowering the diagnostic threshold on the incidence, management and clinical outcome of patients with type 2 myocardial infarction and myocardial injury.

## Methods

### Study population

We identified consecutive patients admitted to our regional cardiac center (Royal Infirmary, Edinburgh, United Kingdom), with plasma cardiac troponin I concentrations  $\geq 50$  ng/L irrespective of clinical presentation during the validation and implementation of a contemporary sensitive troponin assay. We report a pre-specified analysis from a published cohort study evaluating the impact of implementation of a contemporary sensitive troponin assay on patients with suspected acute coronary syndrome.<sup>7</sup> In this analysis we include all patients in whom troponin was measured as part of routine clinical care whether or not they presented with suspected acute coronary syndrome.

Clinical characteristics as described previously<sup>7</sup> including the primary presenting symptom, referral to specialist cardiology services, cardiac investigations, percutaneous or surgical coronary revascularization and the use of medical therapies were obtained through 'TrakCare' (InterSystems Corporation, Cambridge, MA, USA): an electronic patient record system used by all hospitals in National Health Service (NHS) Lothian, United Kingdom. Exclusion criteria included patients admitted for elective non-emergency procedures, patients resident outwith Lothian, and those incomplete hospital records.

### Troponin assay

Plasma troponin I concentrations were measured using the ARCHITECT<sub>STAT</sub> assays (Abbott Laboratories, Abbott Park, IL). The study was divided into two phases: validation and implementation. Whilst plasma troponin was measured using the reformulated sensitive assay throughout both phases, only concentrations above our previous diagnostic threshold ( $\geq 200$

ng/L) were reported in the validation phase, whilst concentrations above the revised diagnostic threshold ( $\geq 50$  ng/L) were reported during the implementation phase.<sup>7</sup>

### **Classification of myocardial infarction**

Patients were classified as having a type 1 myocardial infarction when myocardial necrosis occurred in the context of an isolated presentation with suspected acute coronary syndrome with chest pain or evidence of myocardial ischemia on the electrocardiogram.<sup>1</sup> Patients with symptoms and signs of myocardial ischemia on the electrocardiogram which were thought to be due to either increased oxygen demand or decreased supply (e.g. tachyarrhythmia, hypotension or anemia) and myocardial necrosis, were classified as having a type 2 myocardial infarction. Myocardial injury was defined as evidence of myocardial necrosis in the absence of any clinical features of myocardial ischemia. Myocardial infarction presenting as a sudden unexpected cardiac death (type 3), following percutaneous coronary intervention (type 4) and coronary artery bypass grafting (type 5) were also defined. Each case was reviewed and classified independently by two cardiologists and any discrepancies resolved by consensus through indepth review of source data. Four hundred consecutive patients were classified by two internal medicine physicians to determine the generalisability of classification.

### **Outcomes**

Clinical outcomes were identified using national and local population registries, the General Register of Scotland and TrakCare respectively. The primary outcomes were recurrent type 1 myocardial infarction and all-cause mortality at one year. Recurrent myocardial infarction was defined as admission with chest pain or ST-segment deviation of  $\geq 0.5$  mm with evidence of myocardial necrosis using plasma troponin concentrations of  $\geq 50$  ng/L as the diagnostic

threshold. Secondary outcomes were coronary revascularization, stroke, gastrointestinal bleeding<sup>9</sup> and length of stay.

### **Statistical Analysis**

Summary clinical statistics were compared by type of myocardial infarction, and between implementation and validation phases using Chi-squared, Fisher's exact, Student's *t*- and Mann-Whitney U tests where appropriate. Agreement for the classification of myocardial infarction was estimated using Cohen's kappa. Cox regression models were used to explore competing risks. Cause specific hazard ratios were estimated for type 1 *versus* 2 myocardial infarction and myocardial injury for time to death and time to recurrent myocardial infarction separately with adjustment for age and sex. Analyses were performed in SPSS (IBM Version 20.0.0, USA) and R (Version 2.14.2, Austria).



## Results

We identified 2,929 patients with a peak plasma troponin concentration  $\geq 50$  ng/L of whom 764 met the exclusion criteria (eFigure); 1,171 (54%) were classified as type 1 myocardial infarction, 429 (20%) as type 2 myocardial infarction, 522 (24%) as myocardial injury, and 43 (2%) as type 3-5 myocardial infarction. There was excellent agreement between cardiologists ( $\kappa=0.92$ , 95% CI 0.89-0.95) and internal medicine physicians ( $\kappa=0.87$ , 95% CI 0.82-0.93) for the classification of myocardial infarction.

Lowering the diagnostic threshold from 200 to 50 ng/L identified an additional 257 patients with type 1 myocardial infarction, 239 patients with type 2 myocardial infarction and 335 patients with myocardial injury: a 22%, 56% and 64% increase respectively ( $P<0.001$ ). The incidence rate for type 1, type 2 myocardial infarction, and myocardial injury increased with age (Figure 1).

### Clinical characteristics

Compared to type 1 myocardial infarction, patients with type 2 myocardial infarction or myocardial injury were older, had worse renal function and were more likely to be female (Table 1). Ninety seven percent of patients with type 1 myocardial infarction had a physician diagnosis of acute coronary syndrome, whereas patients with type 2 myocardial infarction or myocardial injury had a wide range of alternative clinical diagnoses (eFigure 2). Majority of patients with type 2 myocardial infarction presented with chest pain and had a clear alternative primary diagnosis. Patients with myocardial injury were more likely to present with dyspnea, syncope, or confusion. The most common conditions predisposing to type 2 myocardial infarction or myocardial injury were tachyarrhythmia, heart failure and respiratory disorders. (Table 1).

Peak troponin concentrations were higher in patients with type 1 myocardial infarction at 2,420 ng/L compared to 140 ng/L and 130 ng/L in patients with type 2 myocardial infarction and myocardial injury respectively. The majority of patients had a  $\geq 20\%$  change in troponin concentration on serial sampling and this was similar across all groups. Patients with type 1 myocardial infarction were more likely to have ST-segment elevation on the electrocardiogram, whereas ST-segment depression and T-wave inversion were more common in patients with type 2 myocardial infarction and myocardial injury. The clinical characteristics of patients with type 1 and type 2 myocardial infarction did not differ between the validation and implementation phases (data not shown).

### **Management during index admission**

Compared to type 1 myocardial infarction, patients with type 2 myocardial infarction or myocardial injury were less likely to be referred to cardiology services, undergo in-patient coronary angiography and revascularization, and discharged on secondary preventative therapies ( $P < 0.01$  for all; Table 2). The median duration of hospital stay was double in patients with type 2 myocardial infarction (median [IQR]; 7 [2-17] days) and myocardial injury (10 [4-23] days) compared to type 1 myocardial infarction (4 [2-7] days;  $P < 0.001$ ) (Table 2).

In patients with troponin concentration of 50-199 ng/L and type 1 myocardial infarction, lowering the diagnostic threshold increased the number of patients referred for a specialist opinion, further investigations and treatments for myocardial infarction ( $P < 0.01$  for all; Figure 2 and eTable 1). Lowering the diagnostic threshold also increased the number of patients with type 2 myocardial infarction or myocardial injury referred to the cardiologists for further

investigation, although the proportion of patients referred was less than for type 1 myocardial infarction, and the use of therapies for myocardial infarction was unchanged.

### Clinical outcomes

Compared to patients with type 1 myocardial infarction, patients with type 2 myocardial infarction were more likely to die (16% *versus* 37%, RR 1.95, 95%CI 1.61-2.37), but less likely to suffer from recurrent myocardial infarction (12% *versus* 6%, RR 0.46, 95%CI 0.31-0.71; Figure 3). Similar risk ratios were obtained for patients with myocardial injury with a higher proportion dead at one year (16% *versus* 37%, RR 2.36, 95%CI 1.99-2.81) and fewer recurrent myocardial infarcts (12% *versus* 4%, RR 0.29, 95%CI 0.18-0.46). Very similar cause specific hazards ratio were seen after adjusting for age and sex for both recurrent myocardial infarction and death (Figure 3).

In patients with troponin concentration of 50-199 ng/L, lowering the diagnostic threshold was associated with a reduction in recurrent myocardial infarction (24% *versus* 12%, RR 0.48, 95%CI 0.27-0.88) in patients with type 1 myocardial infarction, but not in patients with type 2 myocardial infarction or myocardial injury (Figure 2 and eTable 1). Similar reductions were observed for death and recurrent myocardial infarction in patients with type 1 myocardial infarction (31% *versus* 20%, RR 0.64, 95%CI 0.41-0.99), but no change was observed in patients with type 2 myocardial infarction (31% *versus* 27%, RR 0.87, 95%CI 0.59-1.30) or myocardial injury (40% *versus* 34%; RR 0.84, 95%CI 0.61-1.15).

## Discussion

The frequency and clinical implications of type 2 myocardial infarction and myocardial injury in clinical practice is uncertain. Here we have systematically evaluated all patients with elevated plasma troponin concentrations admitted to a regional cardiac center during the validation and implementation of a sensitive troponin assay and have made a number of important and novel observations. First, type 2 myocardial infarction or myocardial injury are as common as type 1 myocardial infarction in clinical practice irrespective of the threshold for diagnosis. The incidence of type 2 myocardial infarction or myocardial injury increases with age and is more common than type 1 myocardial infarction in patients  $\geq 75$  years of age. Second, patients with type 2 myocardial infarction or myocardial injury have worse clinical outcomes than patients with type 1 myocardial infarction with 1 in 3 patients dead at one year. Third, lowering the diagnostic threshold preferentially increases the number of patients identified with type 2 myocardial infarction or myocardial injury. Indeed, for every additional patient reclassified as type 1 myocardial infarction, we identified three patients with type 2 myocardial infarction or myocardial injury. Finally, patients reclassified as type 2 myocardial infarction or myocardial injury remained in hospital longer and underwent more cardiac investigations but, in contrast to type 1 myocardial infarction, were discharged without additional cardiac therapies and clinical outcomes remained poor and unchanged.

The Universal Definition makes a distinction between type 2 myocardial infarction and causes of elevations in plasma troponin resulting in myocardial injury, such as renal failure, heart failure,<sup>11</sup> sepsis<sup>12,13</sup> and myopericarditis,<sup>14</sup> and defines myocardial infarction, regardless of pathobiology, as evidence of myocardial necrosis in the presence of clinical symptoms and signs of myocardial ischemia.<sup>15,16</sup> However, it is clinically challenging to distinguish between patients with type 2 myocardial infarction and myocardial injury because there remains

considerable overlap between how these two clinical entities.<sup>5,6</sup> The consensus document does not provide specific criteria on how to differentiate between these entities in clinical practice and our analysis represents one of the first attempts to do so in consecutive hospitalised patients. Thus, our frequency data may differ from those of others who may have applied a different criteria to define type 1 myocardial infarction and may or may not have had a category for myocardial injury. Accordingly, the frequency of type 2 myocardial infarction in our study of 20% (429/2,165) was lower than the only previous reports where the frequency was 30% (64/701 patients)<sup>17</sup> and 26% (144/553 patients)<sup>18</sup> in unselected hospitalised patients with elevated troponin concentrations. Our analysis is novel in that we distinguish between patients with type 2 myocardial infarction and myocardial injury, and differences in classification may explain the lower rates of type 2 myocardial infarction in our cohort. Perhaps unsurprisingly, type 2 myocardial infarction has been reported to be less frequent (2 to 5%) in highly selected populations with myocardial infarction from randomised controlled trials or registries of patients admitted to cardiac units.<sup>4,19,20</sup> Our patients were widely distributed across medical and surgical specialties, and it is likely selection bias has underestimated the prevalence of type 2 myocardial infarction in these studies.

One of the main strengths of our study is that we identified a group of patients admitted during the validation period in whom plasma troponin concentrations of 50-199 ng/L were reported as normal. This allowed us to assess the impact of implementation of a sensitive troponin assay on the management and clinical outcome of these patients. Lowering the diagnostic threshold for myocardial infarction increased the use of appropriate investigations and treatments in patients with type 1 myocardial infarction. This was associated with a reduction in recurrent myocardial infarction and death consistent with our previous report.<sup>7</sup> In contrast, there was no improvement in the clinical outcome of patients with type 2 myocardial

infarction or myocardial injury despite increased referral to cardiology services and subsequent additional invasive and non-invasive investigations. Approximately one third of patients with type 2 myocardial infarction were dead at one year. These findings are consistent with Saaby *et al.* who observed mortality rates that were two fold higher in patients with type 2 myocardial infarction compared to type 1 myocardial infarction.<sup>21</sup> Importantly, despite more patients being identified as having type 2 myocardial infarction after lowering the diagnostic threshold, the majority of these patients did not receive additional therapies for coronary heart disease. This may represent a missed opportunity to improve outcomes and further prospective studies are required to define the optimal management of patients with type 2 myocardial infarction.

The increased frequency of type 2 myocardial infarction or myocardial injury is likely to be even more marked with the development of the next generation high-sensitivity troponin assays that will permit further lowering of the diagnostic threshold for myocardial infarction.<sup>22-24</sup> These assays are likely to identify an even greater and more disproportionate number of patients with myocardial injury or type 2 myocardial infarction. However, this must not detract from the substantial benefits that high-sensitivity assays will confer for diagnosing patients with type 1 myocardial infarction.<sup>25,26</sup> This underlines the need to provide additional guidance on how to distinguish between myocardial infarction and myocardial injury.<sup>27</sup>

We believe there remains scope for clarification of the diagnostic criteria for type 2 myocardial infarction and that this is necessary to help clinicians adopt the proposed classification. Acute myocardial injury should be the initial diagnosis in all patients with troponin elevations due to supply-demand imbalance including those with chest pain or

evidence of myocardial ischemia. This would be in keeping with many other organ systems, such as acute liver or kidney injury, where similar elevations in tissue enzymes or biomarkers confer major prognostic value, but are not disease specific. In our opinion, type 2 myocardial infarction should be used exclusively in patients where coronary artery disease has contributed to myocardial injury and where there may be opportunities to improve outcomes through medical therapy or coronary revascularization. Selection of patients for further investigation will depend on the mechanism of myocardial injury and the patient's probability of having coronary artery disease.<sup>5</sup>

Despite our careful attempts to classify patients, we were reliant on investigations performed by attending clinicians. Whilst agreement between our adjudicating cardiologists and internal medicine physicians was excellent, we accept that a small proportion of patients with type 2 myocardial infarction or myocardial injury may have been misclassified. Furthermore, we were unable to differentiate between acute and chronic myocardial injury in many patients as serial samples were requested at the discretion of the clinical team and were not routinely obtained in patients without suspected acute coronary syndrome.

In conclusion, we have demonstrated that type 2 myocardial infarction and myocardial injury are now as common as type 1 myocardial infarction in clinical practice. Using a sensitive troponin assay, we identified three patients with type 2 myocardial infarction or myocardial injury for every patient reclassified as type 1 myocardial infarction. Whilst this was associated with better treatment and outcomes in patients with type 1 myocardial infarction, patients with type 2 myocardial infarction or myocardial injury underwent more investigations and utilized additional cardiac services without altering their poor clinical outcome.

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### **Conflict of interest and financial disclosures statement**

ASVS, NLM and SW have received honoraria for Abbott Diagnostics and NLM has acted as a consultant for Beckman-Coulter and Abbott Diagnostics. ASJ has consulted for most of the major diagnostic companies. All other authors have no conflict of interest or financial disclosures to declare.



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## Figure Legends

### **Figure 1. Incidence rate of type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury per 100,000 persons in Lothian stratified by age**

The incidence rate was estimated as the number of events during the total 12-month period divided by the mid-year population estimates for that age-specific stratum.<sup>10</sup> Patients <75 years had a higher incidence of type 1 than type 2 myocardial infarction or myocardial injury (124 *versus* 60 per 100,000 persons) whereas the reverse was true for patients  $\geq 75$  years (750 *versus* 1,008 per 100,000 persons).

### **Figure 2. Cumulative incidence of (a) recurrent myocardial infarction and (b) death in patients with type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury**

Compared to patients with type 1 myocardial infarction, patients with type 2 myocardial infarction or myocardial injury were less likely to be readmitted with myocardial infarction, but were more likely to die at one year. In comparison to patients with type 1 myocardial infarction, more patients with type 2 myocardial infarction (16% *versus* 31%; HR 1.62, 95% CI 1.30-2.04) and myocardial injury (16% *versus* 37%; HR 1.87, 95% CI 1.52- 2.30) were dead, but fewer had recurrent myocardial infarction (12% *versus* 6%; HR 0.40, 95% CI 0.26-0.62 and 12% *versus* 3%; HR 0.24, 95% CI 0.15- 0.40 respectively) at one year. Hazards ratio presented after adjustment for age and sex with type 1 myocardial infarction as referent.

### **Figure 3. Change in the investigation, management and clinical outcomes of patients with type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury following implementation of a sensitive troponin assay**

In patients with troponin concentrations of 50-199 ng/L and type 1 myocardial infarction, lowering the diagnostic threshold increased referrals for a specialist opinion, further investigation and treatments for myocardial infarction ( $P<0.01$  for all). For patients with type 2 myocardial infarction and myocardial injury similar patterns were seen although the absolute magnitude was smaller. In patients with type 1 myocardial infarction, lowering the diagnostic threshold was associated with a significant reduction in recurrent myocardial infarction (absolute risk reduction 12%, 95% CI 3 to 23%) whereas outcomes in patients with type 2 myocardial infarction and myocardial injury remained unchanged. PCI = percutaneous coronary intervention; DAPT = dual anti-platelet therapy. \* $P<0.05$ , \*\*  $P<0.01$ , \*\*\* $P<0.001$

## Sensitive Troponin Assay and the Classification of Myocardial Infarction

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**Abstract:** 295

**Figures and tables:** 5

**Word count:** 2,991

**References:** 25

**Keywords:** troponin, myocardial infarction, type 2, outcomes

**Table 1. Baseline characteristics of patients with type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury**

	Type 1 MI (n=1,171)	Type 2 MI (n=429)	Myocardial injury (n=522)
Age	68 (14)	75 (14)	76 (13)
Male sex, (%)	709 (61%)	222 (52%)	260 (50%)
<b>Presenting symptom, n (%)</b>			
Ischaemic chest pain	1,041 (89%)	217 (51%)	0 (0%)
Dyspnoea	45 (4%)	80 (19%)	172 (33%)
Collapse/syncope	21 (2%)	31 (7%)	94 (18%)
Falls	18 (2%)	40 (9%)	86 (17%)
Confusion	2 (0%)	15 (4%)	23 (4%)
Palpitations	2 (0%)	4 (1%)	18 (3%)
Abdominal pain	6 (1%)	6 (1%)	12 (2%)
Cardiac arrest	14 (1%)	0 (0%)	3 (1%)
<b>Past medical history, n (%)</b>			
Ischemic heart disease	497 (45%)	191 (45%)	186 (36%)
Myocardial infarction	231 (24%)	109 (26%)	107 (21%)
Stroke	92 (8%)	48 (11%)	86 (17%)
Peripheral vascular disease	85 (8%)	29 (7%)	39 (8%)
Previous PCI	153 (15%)	17 (4%)	23 (5%)
Previous CABG	62 (6%)	30 (7%)	32 (6%)
<b>Risk factors, n (%)</b>			
Current smoker	380 (34%)	62 (15%)	73 (14%)
Hypertension	533 (48%)	254 (59%)	303 (59%)
Hyperlipidemia	539 (49%)	177 (42%)	202 (39%)
Diabetes mellitus	185 (17%)	93 (22%)	96 (19%)
<b>Biochemistry</b>			
Hemoglobin, mg/dL	13.3 (2.0)	12.1 (2.5)	12.0 (2.2)
Creatinine, mg/dL	1.2 (0.7)	1.5 (1.2)	1.4 (1.4)
GFR, ml/min	69 (26)	56 (30)	52 (33)
GFR < 30ml/min, %	89 (8%)	67 (16%)	125 (24%)
Cholesterol, mg/dL	185 (50)	166 (51)	171 (53)
Troponin, ng/L	2,420 (270-15,230)	140 (70-660)	130 (60-390)
Change in troponin ≥ 20%	432 (86%)	41 (65%)	41 (79%)
<b>Electrocardiography, no (%)</b>			
ST elevation	427 (38%)	40 (10%)	3 (1%)
ST depression	207 (18%)	152 (36%)	0 (0%)
T-wave inversion	125 (11%)	97 (23%)	13 (3%)
<b>Medication on admission, no (%)</b>			
Aspirin	418 (50%)	222 (56%)	244 (54%)
Clopidogrel	100 (12%)	25 (6%)	26 (6%)
β-blockers	257 (31%)	101 (26%)	111 (25%)
ACE-inhibitors	300 (36%)	136 (34%)	158 (35%)
Statins	384 (47%)	156 (40%)	191 (42%)
Warfarin	35 (4%)	38 (10%)	52 (12%)
Proton pump inhibitors	188 (24%)	127 (33%)	135 (30%)

Values are mean (standard deviation), median (interquartile range) and counts (%). Abbreviations: PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Grafting, TIMI – Thrombolysis in Myocardial Infarction, GFR = Glomerular Filtration Rate, ACE – Angiotensin Converting Enzyme. Conversion factor to SI Units as follows: Hemoglobin = 10, Creatinine = 88.4, Cholesterol = 0.0259).

## Sensitive troponin assay and classification of myocardial infarction

**Table 2. Management and outcomes of patients with type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury**

	Type 1 MI (n = 1,171)	Type 2 MI (n = 429)	Myocardial injury (n = 522)	P-Value/ RR Type 1 versus Type 2	P-Value / RR Type 2 versus myocardial injury
<b>Management, n (%), median (IQR)</b>					
Cardiology referral	1,004 (87%)	181 (43%)	146 (29%)	<.001	<.001
Length of stay, median days (IQR)	4 (2-7)	7 (2 – 17)	10 (4 – 23)	<.001	<.001
<b>Investigations, n (%)</b>					
Echocardiography	340 (30%)	122 (29%)	117 (23%)	0.535	0.042
Exercise tolerance test	29 (3%)	1 (0%)	0 (0%)	0.003	0.451
Angiography	744 (65%)	31 (7%)	19 (4%)	<.001	0.012
<b>Coronary revascularization, n (%)</b>					
PCI	564 (49%)	1 (0%)	3 (1%)	<.001	0.632
CABG	56 (5%)	3 (1%)	3 (1%)	<.001	0.999
<b>Medications on discharge, n (%)</b>					
Aspirin	910 (90%)	166 (49%)	192 (49%)	<.001	0.835
Clopidogrel	831 (80%)	48 (14%)	38 (9%)	<.001	0.052
Dual anti-platelet therapy	789 (76%)	26 (7%)	26 (6%)	<.001	0.547
β-blockers	660 (63%)	124 (36%)	114 (28%)	<.001	0.02
ACE-inhibitors	735 (71%)	135 (39%)	159 (39%)	<.001	0.999
Statins	884 (85%)	152 (44%)	190 (46%)	<.001	0.442
Warfarin	35 (3%)	52 (15%)	61 (15%)	<.001	0.965
Proton pump inhibitors	304 (29%)	135 (39%)	150 (37%)	0.001	0.508
<b>Outcomes, n (%)</b>					
Recurrent MI <sup>a</sup>	141 (12%)	24 (6%)	18 (3%)	<b>0.46 (0.31 – 0.71)</b>	0.62 (0.34 – 1.12)
Death	187 (16%)	134 (31%)	193 (37%)	<b>1.95 (1.61 – 2.37)</b>	1.19 (0.99 – 1.42)
Recurrent MI/death	280 (24%)	144 (34%)	203 (39%)	<b>1.40 (1.19 – 1.66)</b>	1.16 (0.98 – 1.38)
Gastrointestinal bleeding <sup>b</sup>	20 (2%)	11 (3%)	7 (1%)	1.50 (0.73 – 3.11)	0.52 (0.21 – 1.34)
Stroke <sup>c</sup>	24 (2%)	11 (3%)	22 (4%)	1.25 (0.61 – 2.53)	1.64 (0.81 – 3.35)
Coronary revascularization <sup>d</sup>	95 (8%)	5 (1%)	5 (1%)	<b>0.14 (0.06 – 0.35)</b>	0.82 (0.24 – 2.82)

<sup>a</sup> Recurrent type 1 myocardial infarction. <sup>b</sup> Includes type II – V bleeding as defined in the recent consensus statement.<sup>20</sup> <sup>c</sup> Defined as stroke by the attending physician. <sup>d</sup> Coronary revascularization includes both percutaneous coronary intervention and coronary artery bypass grafting. <sup>e</sup> Type 1 myocardial infarction as referent. <sup>f</sup> Type 2 myocardial infarction as referent.



Figure 1

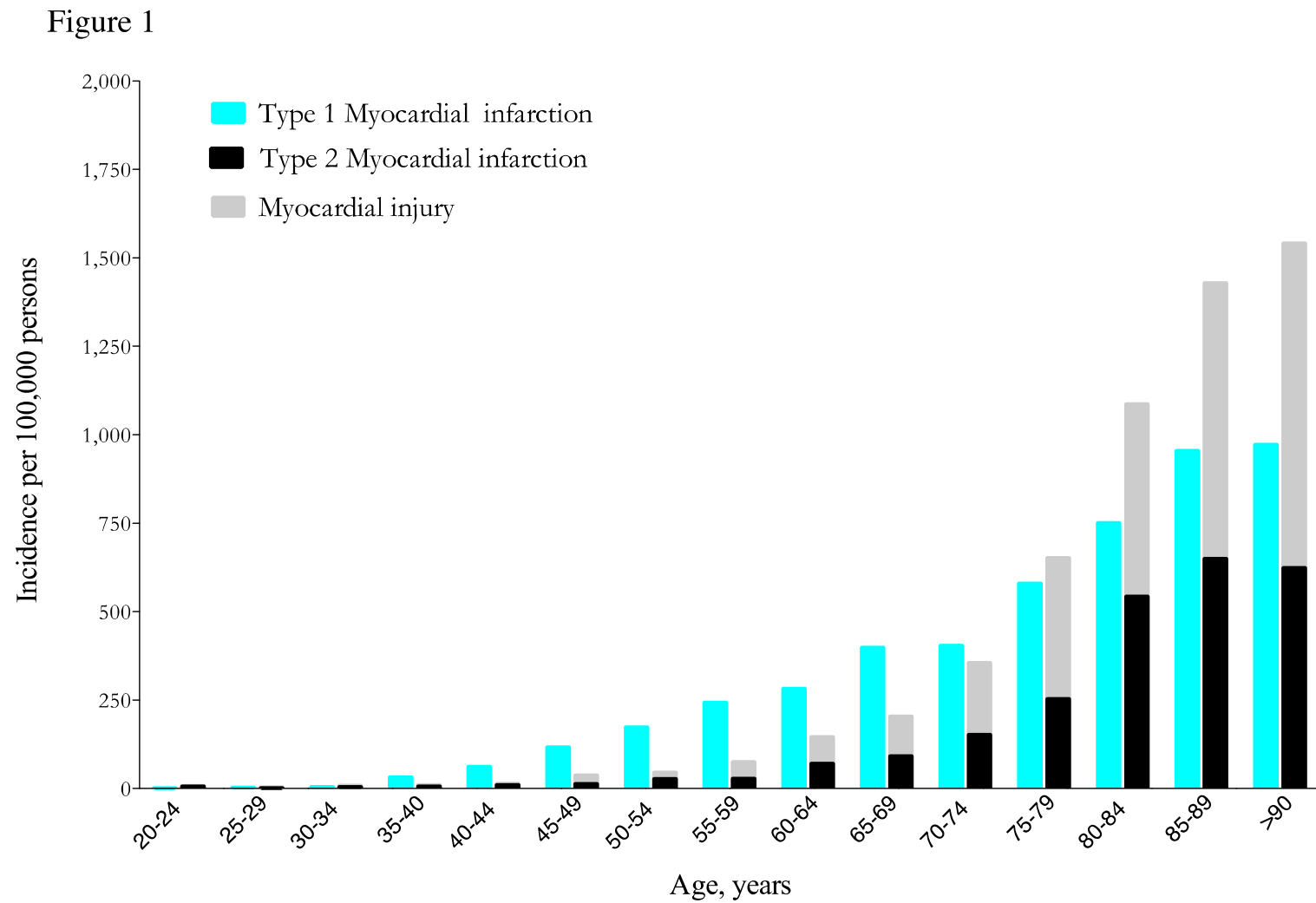
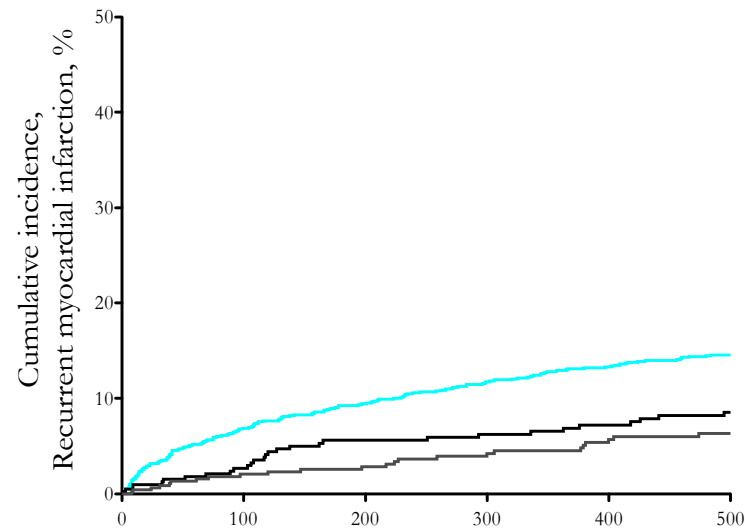


Figure 2

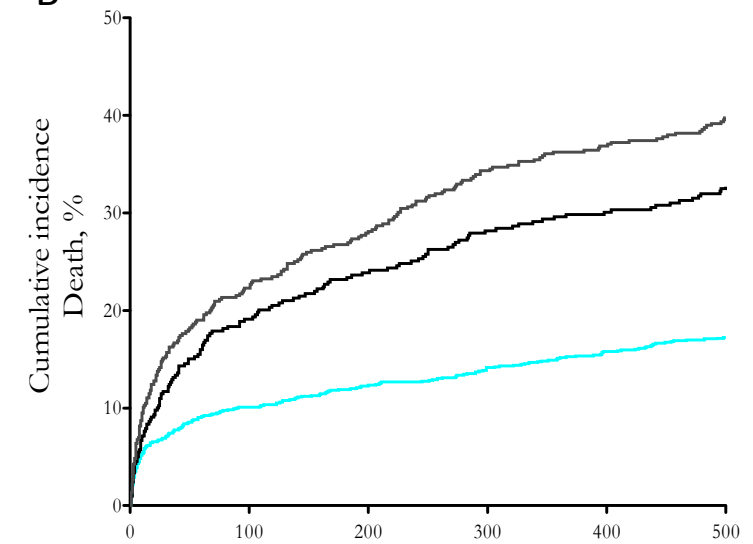
A''



No. at risk

Type 1 myocardial infarction	1,171	989	949	914	886	863
Type 2 myocardial infarction	429	338	317	294	284	271
Myocardial injury	522	397	367	331	315	300

B''

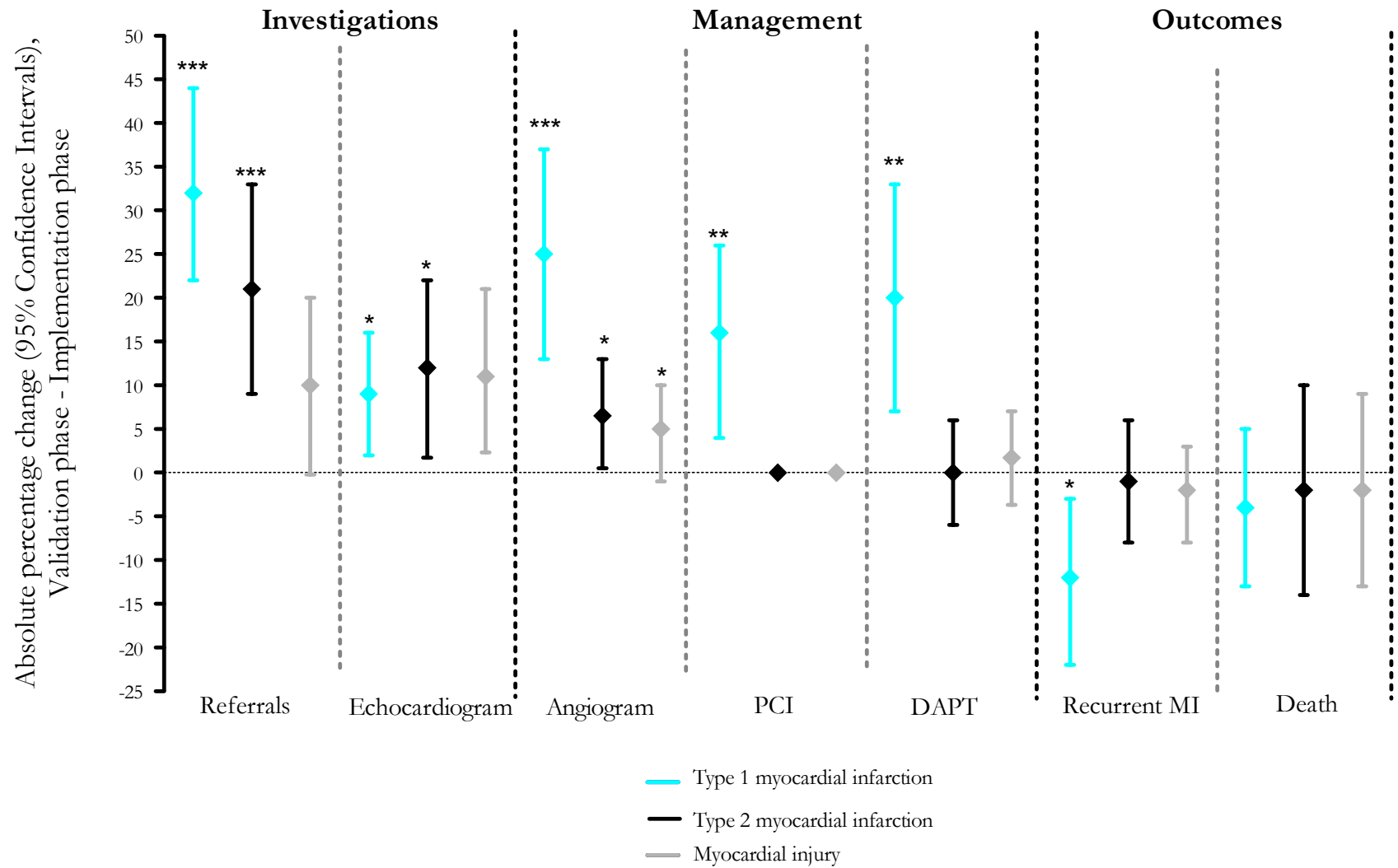


No. at risk

Type 1 myocardial infarction	1,171	1,044	1,018	999	978	960
Type 2 myocardial infarction	429	340	320	302	294	283
Myocardial injury	522	402	373	341	327	311

— Type 1 myocardial infarction  
 — Type 2 myocardial infarction  
 — Myocardial injury

Figure 3



## **Sensitive Troponin Assay and the Classification of Myocardial Infarction**

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## Clinical significance of the manuscript

- Lowering the diagnostic threshold for troponin preferentially increases the number of patients identified with type 2 myocardial infarction or myocardial injury.
- Patients reclassified as type 2 myocardial infarction or myocardial injury remained in hospital for longer and were more likely to undergo cardiac investigations but, in contrast to type 1 myocardial infarction, were discharged without additional cardiac therapies and clinical outcomes remained poor and unchanged

## **Sensitive Troponin Assay and the Classification of Myocardial Infarction**

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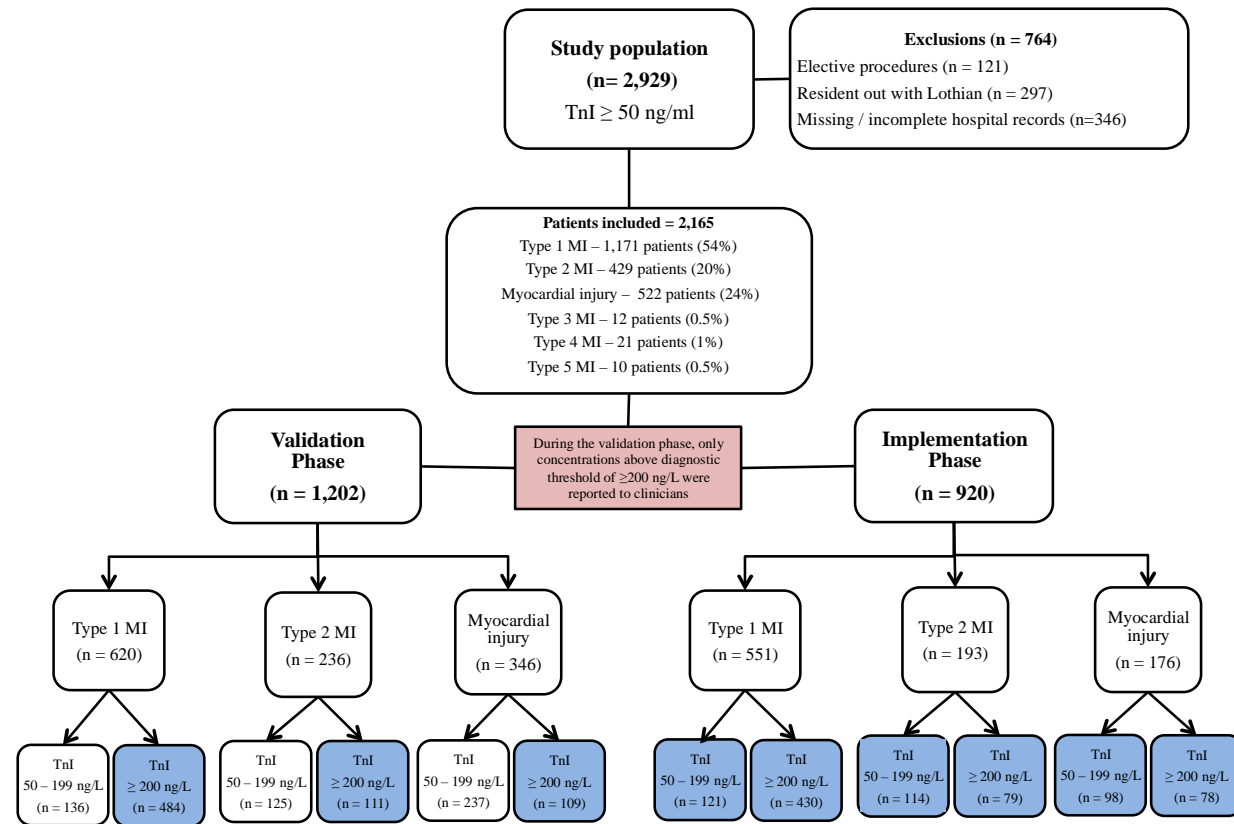
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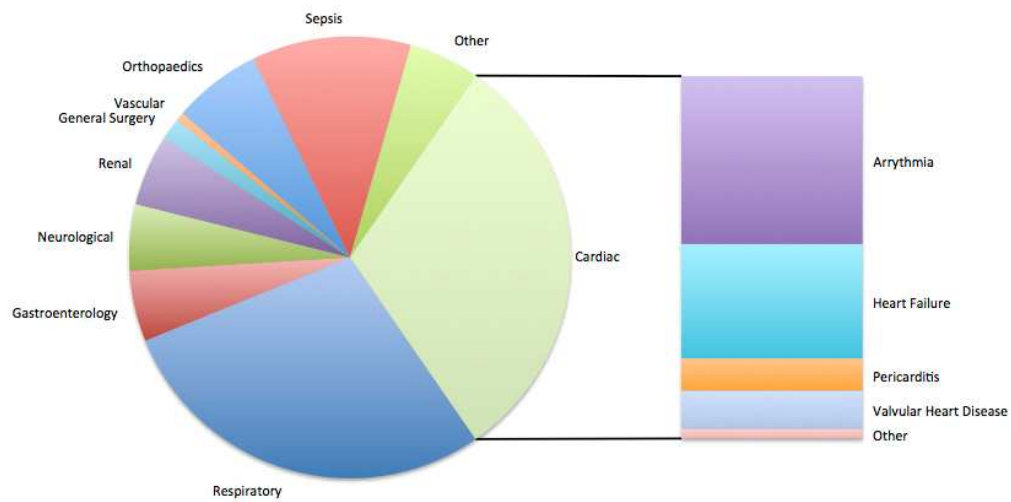
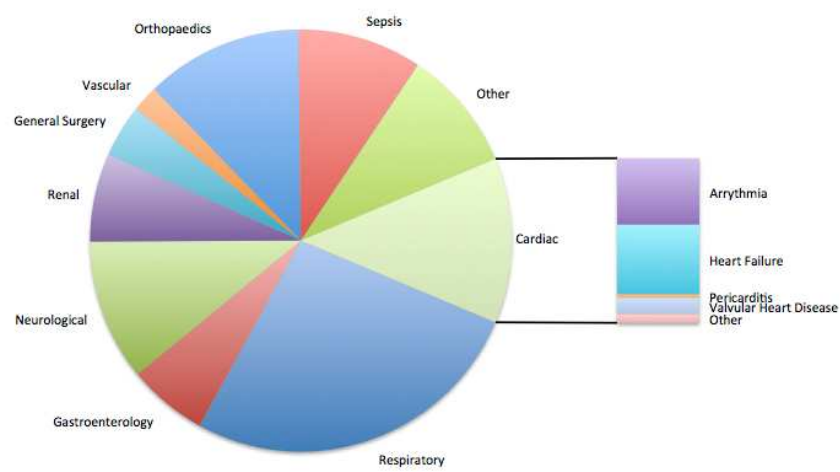
**eFigure 1. CONSORT diagram of study population stratified by infarct type and study phase.** Consecutive patients with plasma troponin I (TnI) concentrations  $\geq 50$  ng/L were identified irrespective of clinical presentation during the validation (1<sup>st</sup> February 2008 to 31<sup>st</sup> July 2008) and implementation (1<sup>st</sup> February 2009 to 31<sup>st</sup> July 2009) of a contemporary sensitive troponin I assay (n=2,929). Exclusion criteria were limited to patients admitted for elective non-emergency procedures, patients who were resident outwith Lothian, and patients with incomplete hospital records. The remaining 2,165 patients were classified as type 1 to type 5 myocardial infarction or myocardial injury. Whilst plasma troponin was measured using a reformulated sensitive assay throughout both phases, only concentrations above a diagnostic threshold of 200 ng/L were reported in the validation phase, whilst concentrations above a revised diagnostic threshold of 50 ng/mL were reported during the implementation phase.

**eFigure 2. Primary diagnosis of patients with type 2 myocardial infarction and myocardial injury.** Patients classified as (a) type 2 myocardial infarction or (b) myocardial injury were a heterogeneous group presenting to a wide range of medical and surgical specialties. Most patients with type 2 myocardial infarction had a cardiac or respiratory diagnosis with heart failure and arrhythmias the most common cause of elevated troponin concentrations.

eFigure 1: CONSORT diagram





**eFigure 2****a) Type 2 myocardial infarction****b) Myocardial injury**

**eTable 1: Clinical investigations, management and outcomes in patients with troponin concentration between 50 and 199 ng/L in patients with type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury**

	<i>Type 1 myocardial infarction</i>			<i>Type 2 myocardial infarction</i>			<i>Myocardial injury</i>		
	Validation (n = 136)	Implementation (n = 121)	P-value/Relative Risk <sup>c</sup> (95% CI)	Validation (n = 125)	Implementation (n = 114)	P-value/ Relative Risk <sup>c</sup> (95% CI)	Validation (n = 237)	Implementation (n = 98)	P-value/ Relative Risk <sup>c</sup> (95% CI)
Cardiology referral	67 (50%)	96 (83%)	<b>&lt;0.001</b>	31 (26%)	53 (48%)	<b>0.001</b>	40 (18%)	27 (28%)	<b>0.043</b>
<b>Investigations, n (%)</b>									
Echocardiography	6 (4%)	16 (13%)	<b>0.014</b>	19 (15%)	31 (27%)	<b>0.023</b>	28 (12%)	23 (24%)	<b>0.007</b>
Exercise tolerance test	6 (4%)	3 (2%)	>0.99	1 (1%)	0 (0%)	0.999	0 (0%)	0 (0%)	-
Angiography	36 (27%)	60 (52%)	<b>&lt;0.001</b>	3 (3%)	10 (9%)	<b>0.032</b>	2 (1%)	5 (5%)	<b>0.025</b>
<b>Coronary revascularisation, n (%)</b>									
PCI	19 (14%)	34 (30%)	<b>0.005</b>	1 (1%)	0 (0%)	0.999	0 (0%)	0 (0%)	-
CABG	7 (5%)	3 (3%)	1.00	1 (1%)	1 (1%)	0.999	0 (0%)	0 (0%)	0.376
<b>Medications on discharge, n (%)</b>									
Aspirin	91 (73%)	95 (85%)	<b>0.038</b>	52 (47%)	53 (54%)	0.366	92 (47%)	35 (43%)	0.595
Clopidogrel	53 (43%)	75 (63%)	<b>0.002</b>	10 (9%)	11 (11%)	0.628	8 (4%)	7 (9%)	0.124
Dual anti-platelet therapy	47 (38%)	65 (58%)	<b>0.003</b>	6 (6%)	5 (5%)	0.896	4 (2%)	3 (4%)	0.418
β-blockers	68 (55%)	67 (60%)	0.511	37 (34%)	37 (37%)	0.573	50 (25%)	23 (28%)	0.572
ACE-inhibitors	64 (52%)	76 (68%)	<b>0.017</b>	39 (36%)	45 (46%)	0.141	70 (35%)	38 (47%)	0.072
Statins	82 (57%)	85 (76%)	0.150	42 (38%)	49 (50%)	0.100	95 (48%)	31 (38%)	0.130
Warfarin	9 (5%)	7 (6%)	0.770	18 (17%)	17 (17%)	0.923	26 (13%)	15 (19%)	0.263
Proton pump inhibitors	23 (23%)	51 (46%)	<b>0.001</b>	41 (38%)	33 (33%)	0.488	60 (31%)	30 (37%)	0.299
<b>12-month outcomes, n (%)</b>									
Recurrent MI <sup>a</sup>	33 (24%)	14 (12%)	<b>0.48 (0.27 - 0.88)</b>	10 (8%)	8 (7%)	0.88 (0.36 - 2.14)	13 (6%)	3 (3%)	0.56 (0.19 - 1.92)
Death	19 (14%)	12 (10%)	0.71 (0.36 - 1.40)	34 (27%)	29 (25%)	0.94 (0.61 - 1.43)	86 (36%)	33 (34%)	0.93 (0.67 - 1.28)
Recurrent MI/death	42 (31%)	24 (20%)	<b>0.64 (0.41 - 0.99)</b>	39 (31%)	31 (27%)	0.87 (0.59 - 1.30)	95 (40%)	33 (34%)	0.84 (0.61 - 1.15)
Gastrointestinal bleeding <sup>b</sup>	2 (2%)	3 (3%)	1.67 (0.29 - 9.92)	2 (2%)	2 (2%)	1.10 (0.16 - 7.66)	3 (1%)	4 (4%)	3.22 (0.73 - 14.14)
Stroke <sup>c</sup>	2 (2%)	1 (1%)	0.56 (0.05 - 6.12)	2 (2%)	3 (3%)	1.10 (0.23 - 5.32)	13 (6%)	3 (3%)	0.56 (0.16 - 1.92)
Coronary revascularization <sup>d</sup>	17 (13%)	15 (12%)	0.99 (0.51 - 1.90)	1 (1%)	1 (1%)	1.10 (0.07 - 17.32)	4 (2%)	0 (0%)	-

Values are mean (standard deviation) median (interquartile range) and counts (%). Abbreviations: ACE – angiotensin converting enzyme, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Grafting. <sup>a</sup> Recurrent type 1 myocardial infarction. <sup>b</sup> Includes type 2 – V bleeding as defined in the recent consensus statement.<sup>20</sup> <sup>c</sup> Defined as stroke by the attending physician. <sup>d</sup> Coronary revascularization includes both percutaneous coronary intervention and coronary artery bypass grafting. <sup>e</sup> Relative risks comparing implementation phase with validation phase as the reference group